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Polymorphisms in genes related to the hypothalamic-pituitary-adrenal axis and antidepressant response – systematic review

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Highlights

- Systematic review on polymorphisms in HPA axis genes and antidepressant response
- No relationship between SNPs in *AVP* and *AVPR1A* and treatment response
- Equivocal findings in terms of *NR3C1*, *NR3C2*, and *FKBP5*
- Specific polymorphisms in *CRHBP, CRHR1*, and *POMC* predicted non-response

Abstract

Objective

Around 50% of depressed patients do not respond to antidepressants. Evidence from familial studies suggests a genetic component to this. This study investigated whether patients with polymorphisms in genes related to the hypothalamic-pituitary-adrenal (HPA) axis were less likely to respond to antidepressants.

Method

EMBASE, MEDLINE, PsycINFO, and the Cochrane Library were searched. Inclusionary criteria were: 1) patients with depression, 2) study of HPA axis-related candidate genes, 3) at least four weeks of antidepressants, and 4) assessment of depressive symptoms dividing patients into non-responders and responders.

Results

Nineteen studies were identified. Non-responders and responders did not differ in single nucleotide polymorphisms (SNPs) in genes encoding arginine vasopressin. Findings were equivocal regarding genes encoding the FK506 binding protein 5 and glucocorticoid and mineralocorticoid receptors. Specific SNPs and haplotypes within genes related to corticotropin-releasing hormone (*CRHBP, CRHR1*) and melanocortins (*POMC*) predicted non-responder status.

Conclusions

Replication studies and additional investigations exploring gene x environment and drug x environment interactions are necessary before pharmacological treatments may be adjusted based on a patient's genetic profile.

Keywords: antidepressant; depression; hypothalamic-pituitary-adrenal axis; polymorphism; treatment response

1. Introduction

Antidepressants are among the most widely used first-line treatments for patients with depressive disorders; however, around 50% of patients are not sufficiently responsive (Cleare et al., 2015). This raises the question of the mechanisms underlying the non-response phenomenon.

Alterations in the stress-responsive hypothalamic-pituitary-adrenal (HPA) axis represent one of the most consistent pathophysiological findings in depressive disorders. They include elevated levels of corticotropin-releasing hormone (CRH; Waters et al., 2015), elevated levels of adrenocorticotropic hormone (ACTH) and cortisol (Stetler and Miller, 2011), reduced glucocorticoid sensitivity (Rohleder et al., 2010), and mineralocorticoid to glucocorticoid receptor imbalance (de Kloet et al., 2007). As for potential origins of these alterations, candidate-gene association studies have shown that polymorphisms in a number of genes related to HPA axis functioning appear to be more frequent in some patients with depressive disorders (Cohen-Woods et al., 2013; Ising and Holsboer, 2006). Among these genes are: *AVPR1A*, coding for an arginine vasopressin (AVP) receptor; *CRH*, *CRHBP*, *CRHR1* and *CRHR2*, coding for CRH, its binding protein and its receptors, respectively; *POMC*, involved in the synthesis of proopiomelanocortin, a precursor of ACTH; *FKBP5*, coding for the FK506-binding protein 5, a co-chaperone of glucocorticoid signalling; and *NR3C1*, a gene coding for the glucocorticoid receptor.

Evidence from meta-analysis suggests that alterations in the HPA axis are related to antidepressant treatment response (Fischer et al., 2017a). Higher cortisol concentrations in particular appear to be linked with non-responses, although only in studies with a particular methodological profile. Given parallel evidence for a familial predisposition towards non-responses to antidepressants (Franchini et al., 1998), the aim of the present study was to investigate whether non-responders to antidepressant treatment can be distinguished from responders by means of genetic HPA axis markers. Based on a previous meta-analysis on single-nucleotide polymorphisms (SNPs) within *FKBP5* and antidepressant response (Zou et al., 2010) it was hypothesised that non-responders would have a higher frequency of specific SNPs and related haplotypes in HPA axis-related genes when compared to responders.

2. Method

2.1 Search for records

Relevant records were identified by systematically searching the Cochrane Library, EMBASE, MEDLINE, and PsycINFO databases from the first available year until January 2018. Key words and exploded subject headings were combined in accordance with the thesaurus of each database. The search string consisted of three components: 1) “HPA axis” and synonyms, including relevant genes (e.g., “*NR3C1*”), 2) “depressive disorder”, including synonyms, and 3) “antidepressant” and synonyms, including the most widely prescribed antidepressants (e.g., “citalopram”). The search was part of a larger systematic search including terms related to anxiety disorders, but these records were not considered for the present research question. All searches were restricted to studies conducted in humans. Only studies published in English, German, Dutch, French, Italian, or Spanish were to be included.

2.2 Screening and study selection

Identified records were screened according to the following inclusionary criteria: 1) adults with a current depressive disorder (i.e., major depressive disorder or persistent depressive disorder) diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD), 2) a candidate-gene study of at least one HPA axis-related gene (i.e., *AVP, AVPR1A*, *AVPR1B*, *CRH*, *CRHR1*, *CRHR2*, *CRHBP*, *FKBP5*, *MC1R, NR3C1*, *NR3C2*, *POMC*), and 3) treatment including at least four weeks of continuous administration of antidepressants (i.e., monoamine oxidase (MAO) inhibitors, tri- or tetracyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), noradrenaline reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors (SNRIs), noradrenaline-dopamine reuptake inhibitors, serotonin-noradrenalin-dopamine reuptake inhibitors), and 4) including a standardised measure of depressive symptoms dividing patients into non-responders and responders or non-remitters and remitters. Studies including bipolar patients were excluded. Comorbidity with somatic diseases, other mental disorders, intake of any medication upon study entry, and intake of medication pro re nata during the study were permitted, but recorded (see risk of bias assessment below). Studies that used more than one class of antidepressants were included, but again, this was noted. Full-text articles were retrieved and checked for relevant results. All article reference sections were reviewed for additional records of potential relevance.

2.3 Extraction of study results

For each retrieved study, information was collected about the sample size, eligibility criteria (e.g., medication use), diagnostic procedures, determination of HPA axis-related polymorphisms, blinding, antidepressant treatment, response and remission rates, and main findings. Risk of bias was estimated by means of a modified version of a quality assessment scale that was used in previous meta-analyses on HPA axis functioning as a predictor of treatment response (see Table 1; Fischer and Cleare, 2017; Fischer et al., 2017a; Fischer et al., 2017b). Seven items were scored on a three-point scale (0-2). The maximum attainable score was thus 14.

3. Results

3.1 Search results

The search yielded 29,893 records, of which 56 were considered of potential interest based on their title or abstract. Of these, 37 were excluded because they were not original research articles (e.g., book chapters), were not conducted in adults, included patients with bipolar disorder, were not candidate-gene studies of HPA axis-related genes, did not administer antidepressants, administered antidepressants for less than four weeks, used augmentation strategies, were retrospective in nature (e.g., cross-sectional comparison of genetic HPA axis-related polymorphisms in patients labelled “treatment resistant” vs. healthy controls), or did not contain results in terms of either treatment non-responders versus responders or non-remitters versus remitters. In the end, N=19 studies were eligible to be included in the systematic review.

3.2 Study characteristics

The main characteristics of the 19 included studies are shown in Tables 2-6. All were published between 2007 and 2015. The sample sizes ranged from 96 to 1719. Almost all patients fulfilled criteria for a major depressive disorder. Virtually no study reported on the prevalence of symptomatic subtypes. In total, 84% of studies excluded comorbidity with major mental disorders, 74% excluded medication intake at study entry, 53% excluded patients with some degree of previous treatment-resistance, and 42% excluded patients with major physical diseases. Polymorphisms in HPA axis

genes were determined by means of different commercially available assays. Citalopram and fluoxetine were the most widely used antidepressants (6 studies each, equalling 64%), followed by escitalopram (4 studies, 21%). Antidepressants were administered from 4 to 14 weeks. The average response rate across studies was 60%, ranging from 43% to 72% (mostly assessed by the Hamilton Rating Scale for Depression; HAMD). The average remission rate was 50%, ranging from 38% to 69%.

3.3 Risk of bias

Quality ratings ranged from 2 to 9, with an average of 6 points (14 points maximum). The highest scores were achieved regarding the inclusionary and exclusionary criteria, which in general tended to be quite restrictive (item 1). Similarly, depressive disorders were diagnosed by clinical psychologists and psychiatrists rather than by students in most cases (item 2). Genetic marker selection, population stratification, minor allele frequencies and information on the Hardy-Weinberg equilibrium were reported by the majority of studies, whereas less than half reported information regarding assay reliability or models of penetrance (item 3). Antidepressant dosage was appropriate in more than half of the studies (item 4). By contrast, several studies failed to report whether response assessors were blind to genotypes (item 6) and statistical analyses were rarely fully adequate (item 7): A power analysis was undertaken in only six studies, only five studies controlled for age and sex, four for intake of medication pro re nata during treatment, and two for baseline symptom severity. Most studies did, however, adjust their results for multiple testing. No study used both clinician-rated and self-reported instruments to assess treatment response (item 5).

3.4 Polymorphisms in genes related to the arginine vasopressin (AVP) system

Three studies looked at polymorphisms in genes related to the AVP system (see Table 1). They were conducted in Chinese, Chilean, African American, European American, and Hispanic patients. A number of SNPs within *AVP*, *AVPR1A*, and *AVPR1B* were determined and patients were treated with different SSRIs and SNRIs for up to 12 weeks. None of the studies found any link between any of these SNPs and treatment response or remission.

- Insert Table 1 here -

3.5 Polymorphisms in genes related to the corticotropin-releasing hormone (CRH) system

Nine studies investigated polymorphisms in genes related to the CRH system (see Table 2). Three of these focused on *CRH*. These studies included patients of African American, European American, Hispanic, or Mexican American ethnicity. There was no link whatsoever between any SNPs and haplotypes located in *CRH* and response or remission after up to 12 weeks of treatment with tricyclic antidepressants, tetracyclic antidepressants, or SSRIs.

Three studies investigated *CRHBP*, coding for the CRH binding protein, in relation to treatment response. Binder et al. (2010) found that African American and Hispanic patients with a particular allele of a SNP in *CRHBP* (rs10473984) had a nearly two-fold higher probability of being a non-responder or non-remitter after up to 12 weeks of treatment with citalopram.

Six studies focused on *CRHR1*, coding for one of the CRH receptors. Geng et al. (2014) in their sample of Chinese patients found one SNP (rs28364032) and three related haplotypes in *CRHR1* to be associated with an up to seven-fold increased risk of non-remission after 8 weeks of treatment with different SSRIs and SNRIs.

Finally, six studies looked at *CRHR2*, coding for another CRH receptor. Wong et al. (2008) found one SNP in *CRHR2* (rs917195) to differ between Mexican American non-responders and responders undergoing 8 weeks of treatment with desipramine, while this did not apply to patients treated with 8 weeks of fluoxetine. Notably, this result was not adjusted for multiple testing. Tiwari et al. (2013) found another SNP in *CRHR2* (rs1076292) to differ between African, European, and Hispanic non-responders and responders to up to 12 weeks of treatment with bupropion. However, this only applied to patients completing treatment and no such association was found with remission status.

- Insert Table 2 here -

3.6 Polymorphisms in genes related to the melanocortin system

Three studies looked at polymorphisms related to the melanocortin system (see Table 3). Two studies analysed *POMC*, coding for a precursor of ACTH. Chang et al. (2015b) found one haplotype

comprising four SNPs within *POMC* to be linked with an up to six-fold increased risk of being a non-remitter after 8 weeks of treatment with escitalopram or mirtazapine.

Wu et al. (2011) was the only study investigating polymorphisms in *MC1R*, coding for one of the melanocortin receptors. In their sample of Mexican American patients, two SNPs (rs2228478, rs2228479) differed between non-remitters and remitters after 8 weeks of treatment with desipramine, but not fluoxetine. However, no correction for multiple testing was applied, rendering this a tentative finding.

- Insert Table 3 here -

3.7 Polymorphisms in the gene coding for the FK506 binding protein 5

Ten studies investigated *FKBP5* (see Table 4). In a mixed sample of patients with Black and White ethnicities, Lekman et al. (2008) found one SNP (rs4713916) located in *FKBP5* to distinguish between non-remitters and remitters to up to 14 weeks of treatment with citalopram; it did not, however, distinguish non-responders from responders. Ellsworth et al. (2013) failed to replicate this finding in patients of White ethnicity undergoing 8 weeks of treatment with citalopram or escitalopram. Similarly, Perlis et al. (2009) did not report any significant findings in terms of the same SNP and responder or remission status in Caucasian patients who were administered duloxetine over the course of 6 weeks. Geng et al. (2014) also did not find any link between the same SNP and response to 8 weeks of treatment with different SSRIs and SNRIs in their Chinese sample.

- Insert Table 4 here -

3.8 Polymorphisms in genes coding for the glucocorticoid and mineralocorticoid receptor

Nine studies investigated polymorphisms related to the glucocorticoid and mineralocorticoid receptor (see Table 5). Eight studies sequenced *NR3C1*, coding for the glucocorticoid receptor. In their study of Japanese patients, Takahashi et al. (2014) found one SNP (rs41423247) in *NR3C1* to differ between non-responders and responders to 6 weeks of fluvoxamine treatment, while it failed to differ between non-remitters and remitters. No differences whatsoever were found for the subgroup of their patients undergoing 6 weeks of milnacipran treatment. Geng et al. (2014) did not find the same SNP to

distinguish between Chinese non-responders and responders to 8 weeks of SSRI or SNRI treatment. Similarly, Ventura-Junca et al. (2014) could not replicate the positive finding in their Chilean sample undergoing 8 weeks of fluoxetine treatment, and neither could Lee et al. (2009) in a Korean sample of patients who were treated with citalopram for 8 weeks.

Paddock et al. (2007) was the only study to sequence *NR3C2*, coding for the mineralocorticoid receptor. This was a sample of patients with Black or White ethnicity and no significant associations between SNPs in *NR3C2* and responder or remitter status after 6 weeks of administering citalopram were reported.

- Insert Table 5 here -

4. Discussion

The systematic review yielded three main findings (see also Table 6 for a summary). First, genes coding for the CRH and melanocortin systems appear to contain a number of SNPs and haplotypes, which are able to predict antidepressant response in depressed patients. Second, findings related to genes coding for FKBP5 and the glucocorticoid and mineralocorticoid receptors are equivocal. Finally, there was a considerable risk of bias, which was mainly due to missing detail on how candidate-gene studies were conducted, a lack of a priori power analyses and statistical adjustment for relevant confounders, and failure to report blinding procedures.

- Insert Table 6 here -

The first finding of this systematic review is that SNPs and haplotypes within *CRHBP*, *CRHR1*, and *POMC* have emerged as particularly powerful predictors of antidepressant response. Binder et al. (2010) found a specific SNP (rs10473984) located in *CRHBP* to distinguish between non-responders and responders to citalopram. This finding was most recently extended by O'Connell et al. (2018), who found another SNP (rs28365143) within *CRHBP* to predict responses to escitalopram and sertraline. Importantly, in the Binder et al. study, the same allele predicting non-response was also linked with

greater serum ACTH concentrations. In addition, Geng et al. (2014) found a SNP (rs28364032) and related haplotypes within *CRHR1* to predict remission after administering various SSRIs and SNRIs, and Chang et al. (2015b) found a haplotype within *POMC* to predict remission status after treatment with escitalopram or mirtazapine. Notably, studies reporting positive findings in terms of the CRH and melanocortin system had a much higher average quality score (7.3 out of 14) when compared to those reporting null-findings (4.5 out of 14), which highlights the need for further research adhering to high standards. When taken together, these findings resonate well with evidence of enhanced CRH (Waters et al., 2015) and ACTH (Stetler and Miller, 2011) levels in patients with depressive disorders; however, not all functional links between these SNPs and HPA axis parameters have yet been established. Evidence for causative effects of these polymorphisms is warranted to increase our knowledge on how exactly genetic variance may affect antidepressant treatment.

The second finding of this systematic review purports that although pharmacogenetic studies focusing on *FKBP5* and *NR3C1* are manifold, results are far from conclusive. In terms of *FKBP5*, Lekman et al. (2008) found a particular SNP (rs4713916) to predict remission status after administering citalopram. This aligns well with the fact that the same SNP resides within a functional region of FKBP5, implying causative links with FKBP5 protein expression (Zou et al., 2010). However, three more recent studies included in the present systematic review were unable to replicate this finding (Ellsworth et al., 2013; Geng et al., 2014; Perlis et al., 2009). While two of these studies (Geng et al., 2014; Perlis et al., 2009) used SNRIs and are thus not directly comparable to the Lekman et al. study, Ellsworth et al. (2013) also administered citalopram and escitalopram. According to the authors, divergent sample characteristics are likely to account for the observed discrepancy. One obvious difference is ethnicity, which in the Lekman et al. study was mixed (Black and White non-Hispanic) whereas Ellsworth et al.'s sample was restricted to individuals of White non-Hispanic ethnicity. Equally conflicting findings were revealed regarding *NR3C1*. Takahashi et al. (2014) found that the Bcl1 polymorphism (rs41423247) separated Japanese non-responders and responders when they received fluvoxamine, while there was no apparent effect on response rates when patients received milnacipran. Three studies investigating the same SNP were unable to replicate this finding (Geng et al., 2014; Lee et al., 2009; Ventura-Junca et al., 2014) and again, ethnic diversity is a likely candidate in explaining these inconsistent findings. Further attempts at replicating the positive findings by Lekman et al. (2008) and Takahashi et al. (2014) in ethnically homogenous samples are thus imperative.

Should the above findings be replicated, it is conceivable for depressed patients with a specific, HPA axis-related genetic predisposition to be less likely to respond to first-line treatments, such as antidepressants. The most likely mechanism translating these variants into non-responses is via measurable alterations in the HPA axis. Indeed, some studies have been successful in linking pre-treatment cortisol concentrations with antidepressant response (Fischer et al., 2017a). In addition, antidepressants have repeatedly been demonstrated to normalise HPA axis functioning (Holsboer, 2000), presumably via modulating glucocorticoid receptor functioning (Anacker et al., 2011). In addition, interactions of the HPA axis with other stress-responsive systems, such as the immune system, may modulate treatment response (Strawbridge et al., 2015), and a more comprehensive account of pre-treatment alterations in stress-responsive bodily systems may thus be necessary to understand the mechanisms contributing to non-responses. However, this would imply a functional role of these polymorphisms in HPA axis functioning, and evidence for this remains outstanding for several of the SNPs identified in this systematic review.

Importantly, the genetic variance within HPA axis-related genes is unlikely to exert its potential influence on treatment response in isolation. Instead, there is a high probability for gene-environment interactions to occur. Some of the included studies have considered this by stratifying patients according to the presence of stressful life events (Chang et al., 2015a; Chang et al., 2015b; Geng et al., 2014). Indeed, Chang et al.'s (2015b) finding of a haplotype within *POMC* to predict non-remission was mainly driven by the subgroup of patients not reporting any stressful life events within the year preceding the current major depressive episode. This aligns well with more recent efforts exploring epigenetic modifications as predictors and modulators of treatment response (Belzeaux et al., 2018). In contrast, Geng et al. (2014) found neither childhood trauma nor stressful life events within the past year to interact with a specific SNP within *CRHR1* to predict remitter status. Further studies may be well-advised to include detailed histories of stressful experiences across the lifespan, and to complement genetic with epigenetic markers of the HPA axis. Related to this, drug-environment interactions should be considered by future research. This is important given that recent data suggest that the effect of antidepressants and psychoactive substances in general are co-determined by environmental factors, such as socioeconomic status or pre-treatment psychological state (Carhart-Harris et al., 2018; Chiarotti et al., 2017).

This is the first systematic review of HPA axis-related polymorphisms and antidepressant treatment response. Strengths of this study include the comprehensive literature search, the fact that we defined a distinct phenotype in terms of treatment response (non-responder vs. responder status), and our rigorous risk of bias assessment. On the other hand, relatively few studies matching our eligibility criteria were identified and a number of methodological issues became apparent during the risk of bias assessment. More specifically, the reporting of SNP assay performance and penetrance models, the use of an adequate dosage of antidepressants, the conducting of an a priori power analysis and adjustment for important confounders was insufficient in several of the included studies. This points to potential reasons for some of the null-findings as reported above, and it is thus strongly recommended that future studies are more vigilant in terms of these issues. Finally, due to the heterogeneity of the included studies it was not possible to integrate findings in a quantitative manner. Further research investigating the same SNPs and haplotypes identified in this review is warranted before a meaningful meta-analysis can be undertaken.

In sum, this systematic review has identified a number of HPA axis-related SNPs that hold the promise of identifying non-responders to antidepressant treatments. The current state of the literature suggests that these are primarily located within genes coding for the CRH and melanocortin systems, while the role of polymorphisms within *FKBP5* and *NR3C1* remains ambiguous. Further large-scale studies including additional HPA axis markers (e.g., DNA methylation, gene expression) and stratifying patients according to their current and past levels of stress and other environmental factors are necessary before additional or alternative treatments should be preferentially considered based on a patient's genetic profile.

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Table 1 Characteristics of identified studies on polymorphisms in genes related to the arginine vasopressin (AVP) system and response to antidepressant treatment

Table 2 Characteristics of identified studies on polymorphisms in genes related to the corticotropin-releasing hormone (CRH) system and response to antidepressant treatment; all positive findings adjusted for multiple testing unless stated otherwise

Table 3 Characteristics of identified studies on polymorphisms in genes related to the melanocortin system and response to antidepressant treatment; all positive findings adjusted for multiple testing unless stated otherwise

Table 4 Characteristics of identified studies on polymorphisms in the FK506 binding protein 5 (FKBP5) gene and response to antidepressant treatment; all positive findings adjusted for multiple testing unless stated otherwise

Table 5 Characteristics of the identified studies on polymorphisms in genes related to the mineralocorticoid and glucocorticoid receptors and response to antidepressant treatment; all positive findings adjusted for multiple testing unless stated otherwise

Table 6 Summary of findings divided by whether they are supportive or non-supportive of a relationship between polymorphisms in genes related to the hypothalamic-pituitary-adrenal axis and response to antidepressant treatment; note that different single nucleotide polymorphisms and haplotypes were investigated across studies (see results section for more details)

Table 1 Characteristics of identified studies on polymorphisms in genes related to the arginine vasopressin (AVP) system and response to antidepressant treatment

Study	Sample	Diagnosis	Gene	Treatment	Response/ remission rate	Main findings	Quality rating
Geng, 2014	N=273 n=164 female n=109 male Age: 39±13 years Ethnicity: Chinese Inclusion: HAMD-17 ≥18 Exclusion: history of substance abuse, schizophrenia, schizoaffective disorder, bipolar disorder, generalised anxiety disorder, panic disorder, obsessive-compulsive disorder, personality disorder, mental retardation, primary organic	Diagnosis: Psychiatric evaluation Subtype: Not stated	*AVPR1A* SNaPshot Multiplex Kit	Different types of SSRIs and SNRIs Dosage: Not stated 8 weeks	55% remitters (HAMD-17 ≤7)	No association between SNPs in *AVPR1A* and remission	8/14

	diseases, pregnancy, lactation, drugs within 2 weeks, electroconvulsive therapy within 6 months						
Ventura-Junca, 2014	N=208 n=201 female n=7 male Age: 43±11 years Ethnicity: Chilean Inclusion: HAMD-17 ≥15 Exclusion: substance abuse, psychotic disorder, bipolar disorder, generalised anxiety disorder, panic disorder, obsessive-compulsive disorder, severe cognitive impairment, medical/neurological illness, acute/chronic infections, abnormal thyroid function, hypertension,	Diagnosis: MINI Subtype: Not stated	*AVP* Restriction fragment length polymorphism strategy	Fluoxetine 20mg/day (weeks 1-3), increasing to 40mg/day (flexible, depending on tolerance) 8 weeks	55% responders (50% reduction HAMD-17) 39% remitters (HAMD-17 ≤7)	No association between SNPs in *AVP* and treatment response or remission	7/14

	pregnancy, breastfeeding, medication within 2 months prior to study, history of treatment-resistant MDD						
Binder, 2010	N=1719 Sex: Not stated Age: 18-75 years Ethnicity: African American, European American, Hispanic Inclusion: HAMD ≥14 and QIDS-C ≥10 Exclusion: psychotic disorder, bipolar disorder, obsessive compulsive disorder, primary eating disorder, pregnant or breastfeeding, intake of citalopram, treatment resistance	Diagnosis: Clinician based Subtype: All non-psychotic	*AVP, AVPR1A, AVPR1B* SNPlex System	Citalopram 20mg/day (weeks 1-3), increasing to 40mg/day (week 4) and 60mg/day (week 6) 4-12 weeks	57% responders (50% reduction QIDS-C) 43% remitters (QIDS-C ≤5), 38% non-remitters (QIDS-C ≥10)	No association between SNPs in *AVP, AVPR1A, AVPR1B*, and treatment response or remission	8/14

AVP = arginine vasopressin, AVPR = arginine vasopressin receptor, HAMD = Hamilton Rating Scale for Depression, MINI = Mini International Neuropsychiatric Interview, QIDS-C = Quick Inventory of Depressive Symptomatology – Clinician-Rated, SCID = Structured Clinical Interview for DSM, SNRI = selective noradrenaline reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors

Table 2 Characteristics of identified studies on polymorphisms in genes related to the corticotropin-releasing hormone (CRH) system and response to antidepressant treatment; all positive findings adjusted for multiple testing unless stated otherwise

Study	Sample	Diagnosis	Gene	Treatment	Response/ remission rate	Main findings	Quality rating
Chang, 2015a	N=149 n=118 female n=31 male Age: 51±16 years Ethnicity: unclear Inclusion: HAMD-21 ≥18 Exclusion: substance dependence, schizophrenia, schizoaffective disorder, bipolar disorder, dementia, serious or unstable medical illness, psychotropic	Diagnosis: SCID Subtype: Not stated	*CRH* SNaPshot Multiplex Kit	Escitalopram (5-40mg) Mirtazapine (15-30mg) 12 weeks	41% remitters (HAMD-21 ≤7)	No association between SNPs or haplotypes in *CRH* and remission	6/14

	medication within 2 weeks						
Geng, 2014	N=273 n=164 female n=109 male Age: 39±13 years Ethnicity: Chinese Inclusion: HAMD-17 ≥18 Exclusion: history of substance abuse, schizophrenia, schizoaffective disorder, bipolar disorder, generalised anxiety disorder, panic disorder, obsessive-compulsive disorder, personality disorder, mental retardation, primary organic diseases, pregnancy, lactation, drugs within 2 weeks, electroconvulsive	Diagnosis: Psychiatric evaluation Subtype: Not stated	*CRHR1, CRHR2* SNaPshot Multiplex Kit	Different types of SSRIs and SNRIs Dosage: Not stated 8 weeks	55% remitters (HAMD-17 ≤7)	One SNP (rs28364032) and three haplotypes in *CRHR1* differed between non-remitters and remitters No association between SNPs in *CRHR2* and remission	8/14

	therapy within 6 months						
Ventura-Junca, 2014	N=208 n=201 female n=7 male Age: 43±11 years Ethnicity: Chilean Inclusion: HAMD-17 ≥15 Exclusion: substance abuse, psychotic disorder, bipolar disorder, generalised anxiety disorder, panic disorder, obsessive-compulsive disorder, sever cognitive impairment, medical/neurological illness, acute/chronic infections, abnormal thyroid function, hypertension, pregnancy,	Diagnosis: MINI Subtype: Not stated	*CRHR1, CRHR2* Restriction fragment length polymorphism strategy	Fluoxetine 20mg (weeks 1-3), increasing to 40mg (flexible, depending on tolerance) 8 weeks	55% responders (50% reduction HAMD-17) 39% remitters (HAMD-17 ≤7)	No association between SNPs in *CRHR1* or *CRHR2* and treatment response or remission	7/14

	breastfeeding, medication within 2 months prior to study, history of treatment-resistant MDD						
Tiwari, 2013	N=319 n=199 female n=120 male Age: 39±12 years Ethnicity: African, European, Mexican Inclusion: HAMD-17 ≥17 or IDS-C ≥25 Exclusion: alcohol or substance abuse, schizophrenia, bipolar disorder, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, eating disorder, seizure disorder,	Diagnosis: Investigator evaluation Subtype: Not stated	*CRHR2* iPLEX Platform	Bupropion (150-450mg) 4-12 weeks	60% responders (50% reduction HAMD-17 or IDS-C) 42% remitters (HAMD-17 ≤7 or IDS-C ≤13)	Only in treatment completers did non-responders and responders differ in a SNP (rs1076292) in *CRHR2* No association between SNPs in *CRHR2* and remission	4/14

	brain injury, unstable medical condition, psychotropic drugs within 2 weeks						
Binder, 2010	N=1719 Sex: Not stated Age: 18-75 years Ethnicity: African American, European American, Hispanic Inclusion: HAMD ≥14 and QIDS-C ≥10 Exclusion: psychotic disorder, bipolar disorder, obsessive compulsive disorder, primary eating disorder, pregnant or breastfeeding, intake of citalopram, treatment resistance	Diagnosis: Clinician based Subtype: All non-psychotic	*CRH, CRHBP, CRHR1, CRHR2* SNPlex System, TaqMan Assay	Citalopram 20mg (weeks 1-3), increasing to 40mg (week 4) and 60mg (week 6) 4-12 weeks	57% responders (50% reduction QIDS-C) 43% remitters (QIDS-C ≤5), 38% non-remitters (QIDS-C ≥10)	One SNP (rs10473984) in *CRHBP* differed between African American non-responders and responders, and between Hispanic non-responders and responders (additive model only for the latter ethnicity) The same SNP differed between African Americans and Hispanic non-remitters and remitters No association between SNPs in *CRH, CRHR1, CRHR2* and treatment response or remission	8/14

Dong, 2009	N=272 n=180 female n=92 male Age: 38±10 years Ethnicity: Mexican American Inclusion: HAMD-21 ≥18 and depressed mood item ≥2 Exclusion: any other mental disorder, suicidal ideation, pregnancy, lactation, current use of medication interfering with electro-encephalography, antidepressant intake within 2 weeks, drug use or alcohol abuse within 3 months, enrolment in psychotherapy, treatment resistance	Diagnosis: SCID Subtype: Not stated	*CRHR1* Sequencing (Big DyeTM)	Desipramine (50-200mg) Fluoxetine (10-40mg) 8 weeks	Remission rate: not stated (HAMD-21 <8)	No association between SNPs in *CRHR1* and remission	5/14

Wong, 2008	N=230 n=154 female n=76 male Age: 21-68 years Ethnicity: Mexican American Inclusion: HAMD-21 ≥18 and depressed mood item ≥2 Exclusion: any other mental disorder except anxiety disorders, suicidal ideation, pregnancy, lactation, current use of medication interfering with electro-encephalography, antidepressant intake within 2 weeks, drug use or alcohol abuse within 3 months, enrolment in psychotherapy, treatment resistance	Diagnosis: Unclear Subtype: Not stated	*CRH, CRHBP, CRHR2* Golden Gate Assay	Desipramine (50-200mg) Fluoxetine (10-40mg) 8 weeks	Responder rate: not stated (50% reduction HAMD-21)	One SNP in *CRHR2* (rs917195) differed between non-responders and responders to desipramine (unadjusted for multiple testing) No association between SNPs in *CRH* or *CRHBP* and treatment response	2/14

Liu, 2007	N=127 n=72 female n=55 male Age: 31±11 years Ethnicity: Chinese Inclusion: HAMD-21 ≥18 Exclusion: recent suicide attempt, substance abuse, schizophrenia, bipolar disorder, generalised anxiety disorder, panic disorder, obsessive compulsive disorder, personality disorder, pregnancy, major medical/neurological disorder, intake of antidepressants within 2 weeks, electroconvulsive therapy within 6 months, current psychotherapy,	Diagnosis: Psychiatric evaluation Subtype: Not stated	*CRHR1* TaqMan Assay	Fluoxetine 20mg (weeks 1-2), up to 40mg 6 weeks	53% responders (50% reduction HAMD-21)	No association between SNPs in *CRHR1* and treatment response	8/14

	previous lack of response to fluoxetine						
Papiol, 2007	N=159 n=124 female n=35 male Age:40±12 years Ethnicity: unclear Inclusion: No criteria Exclusion: bipolar disorder, antidepressants within 2 weeks	Diagnosis: SCID Subtype: unclear	*CHRBP, CRHR1, CRHR2* SNaPshot Multiplex Kit	Citalopram (20-40mg) 4 weeks (response), 12 weeks (remission)	65% responders (50% reduction HAMD-21) 69% remitters (HAMD-21 ≤7)	No association between SNPs in *CRHR2* and treatment response	4/14

CRH = corticotropin releasing hormone, CRHR = corticotropin releasing hormone receptor, CRHRBP = corticotropin releasing hormone binding protein, HAMD = Hamilton Rating Scale for Depression, IDS-C = Inventory of Depressive Symptoms – Clinician-Rated, QIDS-C = Quick Inventory of Depressive Symptomatology – Clinician-Rated, SCID = Structured Clinical Interview for DSM, SNRI = selective noradrenaline reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors

Table 3 Characteristics of identified studies on polymorphisms in genes related to the melanocortin system and response to antidepressant treatment; all positive findings adjusted for multiple testing unless stated otherwise

Study	Sample	Diagnosis	Gene	Treatment	Response/ remission rate	Main findings	Quality rating
Chang, 2015b	N=145 n=114 female n=31 male Age: 51±16 years Ethnicity: unclear Inclusion: HAMD-21 ≥18 Exclusion: schizophrenia, schizoaffective disorder, bipolar disorder, dementia, serious or unstable medical illness, substance abuse within 6 months, psychotropic drug	Diagnosis: SCID Subtype: Not stated	*POMC* SNaPshot Multiplex Kit	Escitalopram (5-40mg) Mirtazapine (15-30mg) 8 weeks	38% remitters (HAMD-21 ≤7)	One haplotype in *POMC* differed between non-remitters and remitters (recessive and co-dominant models)	6/14

	intake within 2 weeks						
Wu, 2011	N=181 Sex: Not stated Age: 21-68 years Ethnicity: Mexican American Inclusion: HAMD-21 ≥18 and depressed mood item ≥2 Exclusion: any other mental disorder except anxiety disorders, suicidal ideation, pregnancy, lactation, current use of medication interfering with electro-encephalography, antidepressant intake within 2 weeks, drug use or alcohol abuse within 3 months,	Diagnosis: Unclear Subtype: Not stated	*MC1R* BigDye Terminator v3.1 Sequencing Kit	Desipramine (50-200mg) Fluoxetine (10-40mg) 8 weeks	61% remitters (HAMD-21 <8)	Two SNPs (rs2228479, rs2228478) in *MC1R* differed between desipramine non-responders and responders (unadjusted for multiple testing)	2/14

	enrolment in psychotherapy, treatment resistance						
Wong, 2008	N=230 n=154 female n=76 male Age: 21-68 years Ethnicity: Mexican American Inclusion: HAMD-21 ≥18 and depressed mood item ≥2 Exclusion: any other mental disorder except anxiety disorders, suicidal ideation, pregnancy, lactation, current use of medication interfering with electro-encephalography, antidepressant	Diagnosis: Unclear Subtype: Not stated	*POMC* Golden Gate Assay	Desipramine (50-200mg) Fluoxetine (10-40mg) 8 weeks	Responder rate: not stated (50% reduction HAMD-21)	No association between SNPs in *POMC* and treatment response	2/14

	intake within 2 weeks, drug use or alcohol abuse within 3 months, enrolment in psychotherapy, treatment resistance

HAMD = Hamilton Rating Scale for Depression, MC1R = melanocortin receptor, POMC = proopiomelanocortin, SCID = Structured Clinical Interview for DSM

Table 4 Characteristics of identified studies on polymorphisms in the FK506 binding protein 5 (FKBP5) gene and response to antidepressant treatment; all positive findings adjusted for multiple testing unless stated otherwise

Study	Sample	Diagnosis	Gene	Treatment	Response/ remission rate	Main findings	Quality rating
Geng, 2014	N=273 n=164 female n=109 male Age: 39±13 years Ethnicity: Chinese Inclusion: HAMD-17 ≥18 Exclusion: history of substance abuse, schizophrenia, schizoaffective disorder, bipolar disorder, generalised anxiety disorder, panic disorder, obsessive-compulsive disorder, personality disorder, mental retardation, primary organic diseases,	Diagnosis: Psychiatric evaluation Subtype: Not stated	*FKBP5* Multiplex SNaPshot System	Different types of SSRIs and SNRIs Dosage: Not stated 8 weeks	55% remitters (HAMD-17 ≤7)	No association between SNPs in *FKBP5* and remission	8/14

	pregnancy, lactation, drugs within 2 weeks, electroconvulsive therapy within 6 months						
Ventura-Junca, 2014	N=208 n=201 female n=7 male Age: 43±11 years Ethnicity: Chilean Inclusion: HAMD-17 ≥15 Exclusion: substance abuse, psychotic disorder, bipolar disorder, generalised anxiety disorder, panic disorder, obsessive-compulsive disorder, sever cognitive impairment, medical/neurological illness, acute/chronic infections, abnormal thyroid function, hypertension, pregnancy, breastfeeding,	Diagnosis: MINI Subtype: Not stated	*FKBP5* Restriction fragment length polymorphism strategy	Fluoxetine 20mg (weeks 1-3), increasing to 40mg (flexible, depending on tolerance) 8 weeks	55% responders (50% reduction HAMD-17) 39% remitters (HAMD-17 ≤7)	No association between SNPs in *FKBP5* and treatment response or remission	7/14

	medication within 2 months prior to study, history of treatment-resistant MDD						
Ellsworth, 2013	N=512 Sex: Not stated Age: Not stated Ethnicity: White non-Hispanic Inclusion: HAMD ≥14 Exclusion: bipolar disorder	Diagnosis: Not stated Subtype: All non-psychotic	*FKBP5* BeadXpress System	Citalopram (20mg, up to 40mg at week 4) Escitalopram (10mg, up to 20mg at week 4) 8 weeks	Responder rate: not stated (50% reduction QIDS-C) Remitter rate: not stated (QIDS-C ≤5)	No association between SNPs in *FKBP5* and treatment response or remission	4/14
Tiwari, 2013	N=319 n=199 female n=120 male Age: 39±12 years Ethnicity: African, European, Mexican Inclusion: HAMD-17 ≥17 or IDS-C ≥25	Diagnosis: Investigator evaluation Subtype: Not stated	*FKBP5* iPLEX Platform	Bupropion (150-450mg) 4-12 weeks	60% responders (50% reduction HAMD-17 or IDS-C) 42% remitters (HAMD-17 ≤7 or IDS-C ≤13)	No association between SNPs in *FKBP5* and treatment response or remission	4/14

	Exclusion: alcohol or substance abuse, schizophrenia, bipolar disorder, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, eating disorder, seizure disorder, brain injury, unstable medical condition, psychotropic drugs within 2 weeks						
Perlis, 2009	N=250 n=158 female n=92 male Age: 44±13 years Ethnicity: Caucasian Inclusion: HAMD-17 ≥15 Exclusion: current mental disorder except dysthymia or anxiety disorders, history of psychosis, bipolar disorder, suicidal risk,	Diagnosis: MINI Subtype: Not stated	*FKBP5* iPlex Platform	Duloxetine 30-60mg (week 1), 60mg (weeks 2-6) 6 weeks	51% responder (50% reduction HAMD-17) 44% remitter (HAMD-17 ≤7)	No association between SNPs in *FKBP5* and treatment response or remission	6/14

	serious medical illness, electroconvulsive therapy within 12 months, treatment with MAO inhibitors within 2 weeks, fluoxetine within 4 weeks, substance abuse within 6 months, change in psychotherapy, treatment resistant depression, lack of response to duloxetine						
Uher, 2009	N=811 n=514 female n=297 male Age: 43±12 years Ethnicity: European Inclusion: major depressive episode of at least moderate severity Exclusion: substance abuse, family history of bipolar disorder or schizophrenia, history of (hypo)manic episode,	Diagnosis: SCAN Subtype: Not stated	*FKBP5* SNPlex System	Escitalopram (10mg increasing to 15mg by week 2, with further increasing up to 30mg) Nortriptyline (50mg increasing to 100mg by week 2, with further increasing up to 200mg) 12 weeks	Responder rate: not stated (50% reduction HAMD-17)	No association between SNPs in *FKBP5* and treatment response or remission	5/14

	schizophrenia, mood incongruent psychotic symptoms, primary organic disease, pregnancy, MAO inhibitors or fluoxetine within 2 weeks, history of non-response to study medication						
Lekman, 2008	N=1370 Sex: Not stated Age: 18-75 years Ethnicity: Black, White Hispanic, White non-Hispanic, Other Inclusion: HAMD-17 ≥14 and QIDS-C ≥10 Exclusion: bipolar disorder, schizophrenia, schizoaffective disorder, current obsessive compulsive disorder, primary eating disorder, pregnancy, intake of citalopram within 7 days, treatment resistance	Diagnosis: Clinician based Subtype: All non-psychotic	*FKBP5* TaqMan Assay	Citalopram Dosage: Not stated 6 to 14 weeks	70% responders (50% reduction QIDS-C), 30% non-responders (<40% reduction QIDS-C) 53% remitters (QIDS-C ≤5), 34% non-remitters (QIDS-C ≥10)	One SNP (rs4713916) in *FKBP5* differed between non-remitters and remitters No association between SNPs in *FKBP5* and treatment response	7/14

Paddock, 2007	N=935 Sex: Not stated Age: 18-75 years Ethnicity: Black, White Non-Hispanic Inclusion: HAM-D ≥14 and QIDS-C ≥10 Exclusion: primary diagnosis of bipolar, psychotic, obsessive-compulsive or eating disorder, pregnancy, breastfeeding, history of nonresponse to citalopram	Diagnosis: Clinician based Subtype: All non-psychotic	*FKBP5* BeadArray Platform	Citalopram 20mg (weeks 1-3), increasing to 40mg (week 4) and 60mg (week 6) 6 weeks	72% responders (50% reduction QIDS-C), non-responder rate: 28% (≤40% reduction QIDS-C) Remitter rate: not stated (QIDS-C ≤5), non-remitter rate: not stated (QIDS-C ≥10)	No association between SNPs in *FKBP5* and treatment response or remission	7/14
Papiol, 2007	N=159 n=124 female n=35 male Age:40±12 years Ethnicity: unclear Inclusion: No criteria	Diagnosis: SCID Subtype: unclear	*FKBP5* TaqMan Assay	Citalopram (20-40mg) 4 weeks (response), 12 weeks (remission)	65% responders (50% reduction HAMD-21) 69% remitters (HAMD-21 ≤7)	No association between SNPs in *FKBP5* and treatment response or remission	4/14

	Exclusion: bipolar disorder, antidepressants within 2 weeks						
Tsai, 2007	N=125 n=69 female n=56 male Age: 42±16 years Ethnicity: Chinese Inclusion: HAMD-21 ≥18 Exclusion: substance abuse, schizophrenia, bipolar disorder, generalised anxiety disorder, panic disorder, obsessive-compulsive disorder, major medical/neurological disorder, antidepressants within 2 weeks	Diagnosis: Psychiatric evaluation Subtype: Not stated	*FKBP5* Restriction enzyme	Fluoxetine (20mg) 4 weeks	43% responders (50% reduction HAMD-21)	No association between SNP in *FKBP5* and treatment response or remission	9/14

FKBP = FK506 binding protein, HAMD = Hamilton Rating Scale for Depression, MAO = monoamine oxidase inhibitor, MINI = Mini-International Neuropsychiatric Interview, QIDS-C = Quick Inventory of Depressive Symptomatology – Clinician-Rated, SNRI = selective noradrenaline reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors

Table 5 Characteristics of the identified studies on polymorphisms in genes related to the mineralocorticoid and glucocorticoid receptors and response to antidepressant treatment; all positive findings adjusted for multiple testing unless stated otherwise

Study	Sample	Diagnosis	Gene	Treatment	Response/ remission rate	Main findings	Quality rating
Geng, 2014	N=273 n=164 female n=109 male Age: 39±13 years Ethnicity: Chinese Inclusion: HAMD-17 ≥18 Exclusion: history of substance abuse, schizophrenia, schizoaffective disorder, bipolar disorder, generalised anxiety disorder, panic disorder, obsessive-compulsive disorder, personality disorder, mental retardation, primary organic diseases,	Diagnosis: Psychiatric evaluation Subtype: Not stated	*NR3C1* Multiplex SNaPshot System	Different types of SSRIs and SNRIs Dosage: Not stated 8 weeks	55% remitters (HAMD-17 ≤7)	No association between SNPs in *NR3C1* and remission	8/14

	pregnancy, lactation, drugs within 2 weeks, electroconvulsive therapy within 6 months						
Takahashi, 2014	N=160 n=94 female n=66 male Age: 50±13 years Ethnicity: Japanese Inclusion: MADRS ≥21 Exclusion: any other mental disorder, severe medical disorder, psychotropic drugs within 2 weeks	Diagnosis: Not stated Subtype: Not stated	*NR3C1* Restriction fragment length polymorphism strategy	Fluvoxamine (50mg, increasing to 100mg by week 2, and 200mg by week 3) Milnacipran (50mg, increasing to 100mg by week 2) 6 weeks	65% responder (50% reduction MADRS) 56% remitters (MADRS <10)	One SNP (rs41423247) in *NR3C1* differed between fluvoxamine non-responders and responders No association between the same SNP and remission	6/14
Ventura-Junca, 2014	N=208 n=201 female n=7 male Age: 43±11 years Ethnicity: Chilean	Diagnosis: MINI Subtype: Not stated	*NR3C1* Restriction fragment length polymorphism strategy	Fluoxetine 20mg/day (weeks 1-3), increasing to 40mg/day (flexible, depending on tolerance)	55% responders (50% reduction HAMD-17) 39% remitters (HAMD-17 ≤7)	No association between SNPs in *NR3C1* and treatment response or remission	7/14

	Inclusion: HAMD-17 ≥15 Exclusion: substance abuse, psychotic disorder, bipolar disorder, generalised anxiety disorder, panic disorder, obsessive-compulsive disorder, sever cognitive impairment, medical/neurological illness, acute/chronic infections, abnormal thyroid function, hypertension, pregnancy, breastfeeding, medication within 2 months prior to study, history of treatment-resistant MDD			8 weeks			
Tiwari, 2013	N=319 n=199 female n=120 male Age: 39±12 years	Diagnosis: Investigator evaluation Subtype: Not stated	*NR3C1* iPLEX Platform	Bupropion (150-450mg) 4-12 weeks	60% responders (50% reduction HAMD-17 or IDS-C)	No association between SNPs in *NR3C1* and treatment response or remission	4/14

	Ethnicity: African, European, Mexican Inclusion: HAMD-17 ≥17 or IDS-C ≥25 Exclusion: alcohol or substance abuse, schizophrenia, bipolar disorder, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, eating disorder, seizure disorder, brain injury, unstable medical condition, psychotropic drugs within 2 weeks				42% remitters (HAMD-17 ≤7 or IDS-C ≤13)		
Lee, 2009	N=96 n=70 female n=26 male Age: 49±16 years Ethnicity: Korean Inclusion: HAMD-21 ≥17	Diagnosis: SCID Subtype: Not stated	*NR3C1* Restriction enzyme	Citalopram (20mg, up to 60mg between weeks 2 and 8) 8 weeks	63% responders (50% reduction HAMD-21)	No association between SNPs in *NR3C1* and treatment response	6/14

	Exclusion: any other mental disorder, neurological diseases, chronic diseases other than diabetes and hypertension, drug intake within 2 weeks						
Perlis, 2009	N=250 n=158 female n=92 male Age: 44±13 years Ethnicity: Caucasian Inclusion: HAMD-17 ≥15 Exclusion: current mental disorder except dysthymia or anxiety disorders, history of psychosis, bipolar disorder, suicidal risk, serious medical illness, electroconvulsive therapy within 12 months, treatment with MAO inhibitors within 2 weeks, fluoxetine within	Diagnosis: MINI Subtype: Not stated	*NR3C1* iPlex Platform	Duloxetine 30-60mg (week 1), 60mg (weeks 2-6) 6 weeks	51% responder (50% reduction HAMD-17) 44% remitter (HAMD-17 ≤7)	No association between SNPs in *NR3C1* and treatment response or remission	6/14

	4 weeks, substance abuse within 6 months, change in psychotherapy, treatment resistant depression, lack of response to duloxetine						
Uher, 2009	N=811 n=514 female n=297 male Age: 43±12 years Ethnicity: European Inclusion: major depressive episode of at least moderate severity Exclusion: substance abuse, family history of bipolar disorder or schizophrenia, history of (hypo)manic episode, schizophrenia, mood incongruent psychotic symptoms, primary organic disease, pregnancy, MAO inhibitors or fluoxetine	Diagnosis: SCAN Subtype: Not stated	*NR3C1* SNPlex System	Escitalopram (10mg increasing to 15mg by week 2, with further increasing up to 30mg) Nortriptyline (50mg increasing to 100mg by week 2, with further increasing up to 200mg) 12 weeks	Responder rate: not stated (50% reduction HAMD-17)	No association between SNPs in *NR3C1* and treatment response or remission	5/14

	within 2 weeks, history of non-response to study medication						
Wong, 2008	N=230 n=154 female n=76 male Age: 21-68 years Ethnicity: Mexican American Inclusion: HAMD-21 ≥18 and depressed mood item ≥2 Exclusion: any other mental disorder except anxiety disorders, suicidal ideation, pregnancy, lactation, current use of medication interfering with electro-encephalography, antidepressant intake within 2 weeks, drug use or alcohol abuse within 3 months, enrolment in	Diagnosis: Unclear Subtype: Not stated	*NR3C1* Golden Gate Assay	Desipramine (50-200mg) Fluoxetine (10-40mg) 8 weeks	Responder rate: not stated (50% reduction HAMD-21)	No association between SNPs in *NR3C1* and treatment response	2/14

	psychotherapy, treatment resistance						
Paddock, 2007	N=935 Sex: Not stated Age: 18-75 years Ethnicity: Black, White Non-Hispanic Inclusion: HAM-D ≥14 and QIDS-C ≥10 Exclusion: primary diagnosis of bipolar, psychotic, obsessive-compulsive or eating disorder, pregnancy, breastfeeding, history of nonresponse to citalopram	Diagnosis: Clinician based Subtype: All non-psychotic	*NR3C2* BeadArray Platform	Citalopram 20mg (weeks 1-3), increasing to 40mg (week 4) and 60mg (week 6) 6 weeks	72% responders (50% reduction QIDS-C), non-responder rate: 28% (≤40% reduction QIDS-C) Remitter rate: not stated (QIDS-C ≤5), non-remitter rate: not stated (QIDS-C ≥10)	No association between SNPs in *NR3C2* and treatment response or remission	7/14

HAMD = Hamilton Rating Scale for Depression, IDS-C = Inventory of Depressive Symptoms – Clinician-Rated, MADRS = Montgomery-Asberg Depression Rating Scale, MINI = Mini-International Psychiatric Interview, NR3C1 = glucocorticoid receptor, NR3C2 = mineralocorticoid receptor, QIDS-C = Quick Inventory of Depressive Symptomatology – Clinician-Rated, SCAN = schedules for clinical assessment in neuropsychiatry interview, SCID = Structured Clinical Interview for DSM, SNRI = selective noradrenaline reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors

Table 6 Summary of findings divided by whether they are supportive or non-supportive of a relationship between polymorphisms in genes related to the hypothalamic-pituitary-adrenal axis and response to antidepressant treatment; note that different single nucleotide polymorphisms and haplotypes were investigated across studies (see results section for more details)

System	Supportive	Non-supportive
Arginine vasopressin		No association between *AVP* and response or remission (Binder, 2010; Ventura-Junca, 2014)
		No association between *AVPR1A* and response (Binder, 2010) or remission (Binder, 2010; Geng, 2014)
		No association between *AVPR1B* and response or remission (Binder, 2010)
Corticotropin-releasing hormone		No association between *CRH* and response (Binder, 2010, Wong, 2008) or remission (Binder, 2010; Chang, 2015a)
	Association between *CRHR1* and remission (Geng, 2014)	No association between *CRHR1* and response (Binder, 2010; Liu, 2007; Ventura-Junca, 2014) or remission (Binder, 2010; Dong, 2009; Ventura-Junca, 2014)
	Association between *CRHR2* and response in treatment completers (Tiwari, 2013)	No association between *CRHR2* and response (Binder, 2010; Papiol, 2007; Ventura-Junca, 2014) or remission (Binder, 2010; Geng, 2014; Tiwari, 2013; Ventura-Junca, 2014)
	Association between *CRHBP* and response and remission (Binder, 2010)	No association between *CRHBP* and response (Wong, 2008)
Melanocortin	Association between *POMC* and remission (Chang, 2015b)	No association between *POMC* and response (Wong, 2008)
FK506 binding protein 5	Association between *FKBP5* and remission (Lekman, 2008)	No association between *FKBP5* and response (Ellsworth, 2013; Lekman, 2008; Paddock, 2007; Papiol, 2007; Perlis, 2009; Tiwari, 2013; Tsai, 2007; Uher, 2009; Ventura-Junca, 2014) or remission (Ellsworth, 2013; Geng, 2014; Paddock, 2007; Papiol,

		2007; Perlis, 2009; Tiwari, 2013; Tsai, 2007; Uher, 2009; Ventura-Junca, 2014)
Glucocorticoid and mineralocorticoid receptor	Association between *NR3C1* and response (Takahashi, 2014)	No association between *NR3C1* and response (Lee, 2009; Paddock, 2007; Perlis, 2009; Tiwari, 2013; Uher, 2009; Ventura-Junca, 2014; Wong, 2008) or remission (Geng, 2014; Paddock, 2007; Perlis, 2009; Takahashi, 2014; Tiwari, 2013; Uher, 2009; Ventura-Junca, 2014) No association between *NR3C2* and response or remission (Paddock, 2007)

AVP = arginine vasopressin, AVPR = arginine vasopressin receptor, CRH = corticotropin releasing hormone, CRHR = corticotropin releasing hormone receptor, CRHRBP = corticotropin releasing hormone binding protein, FKBP = FK506 binding protein, NR3C1 = glucocorticoid receptor, NR3C2 = mineralocorticoid receptor, MC1R = melanocortin receptor, POMC = proopiomelanocortin

Supplement and Table legends

Supplement 1 Scale to assess risk of bias in candidate-gene studies of genes related to the hypothalamic-pituitary-adrenal (HPA) axis and their relationship to antidepressant treatment response; modified from Fischer and Cleare (2017), Fischer, Macare and Cleare (2017), and Fischer et al. (2017)